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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

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31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/146,783	DEACON ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *50,66,67,123 and 126-152* is/are pending in the application.

4a) Of the above claim(s) *137-152* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,66,67,123 and 126-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Office Action

37 C.F.R. § 1.114

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 15 October, 2002, has been entered.

Status of the Claims

2. Claims 50, 66, 67, 123, 126-136 were amended and new claims 137-152 introduced. Applicants are reminded that pursuant to M.P.E.P. § 818.02(a) where claims to another invention are properly added and entered in the application before an action is given, they are treated as original claims for purposes of restriction only. The claims originally presented and acted upon by the Office on their merits determine the invention elected by an applicant in the application, and in any request for continued examination (RCE) which has been filed for the application. Subsequently presented claims to an invention other than that acted upon should be treated as provided in M.P.E.P. § 821.03. Accordingly, newly submitted claims 137-152 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly presented claims are directed toward immunogenic compositions and methods of immunizing a host which differ from the originally presented claims which are directed toward vaccine compositions and methods of vaccinating a host. The newly presented claims are directed toward different compositions and methods that accomplish different scientific objectives (e.g.,

induction of immune responses v. induction of therapeutic or prophylactic immune responses). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 137-152 are withdrawn from further consideration as being directed towards a nonelected invention (refer to 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03). Claims 49, 50, 66, 67, 85, and 120-136 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

3. Claims 50 is vague and indefinite for referencing immune responses in both humans and primates. The term primates encompasses monkeys, apes, and humans.[1] Moreover, the claims are directed toward methods of vaccination against the development of AIDS and AIDS-associated pathologies. Non-human primates are not the natural target of the human immunodeficiency virus type 1 (HIV-1) and do not normally develop AIDS or AIDS-related pathologies. Thus, their inclusion in the claim language is confusing. Appropriate correction is required.

4. Claims 122, 124, 129, and 134 are rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims include the limitation "about 10 nucleotides" which is ambiguous since the precise metes and bounds of the subject matter desired cannot be readily ascertained. For instance, do the claims encompass a deletion of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides? Appropriate amendment of the claim language is required.

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[1] Primate: The highest order of mammals, including humans, monkeys, and lemurs. [L. *primus*, first]. Stedman's Medical Dictionary, 27th Edition, Lippincott Williams & Wilkins, 2000.

35 U.S.C. § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 49, 50, 66, 67, 85, and 120-136, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods of vaccinating individuals against AIDS or AIDS related pathologies by administering a non-pathogenic isolate of HIV-1 comprising a *nef* deletion. The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The prior art teaches that many viral and host factors contribute to the pathogenicity of any given isolate. However, deciphering the molecular viral and cellular determinants

contributing to this process has been quite problematic and the disclosure fails to provide any illumination concerning this topic. The problem of addressing this question was addressed by Kirchhoff *et al.* (1995), who PCR-amplified the *nef* coding region from HIV-1-infected long term nonprogressors. Although the authors identified a single patient with reproducible deletions in *nef*, the authors emphasized that these results should be interpreted with considerable caution:

> In this report, we describe a particular HIV-1 gene defect associated with the absence of disease progression in a single patient. Our results, and those of Huang *et al.*,[17] suggest that **deletions in *nef* may not be a common explanation for the absence of progression and that different factors are likely to contribute in other patients. Viral factors that could contribute include different types of mutations in a wide variety of viral genetic elements.** Viral and host factors cannot be dissociated from each other, since an effective immune response is an essential feature of nonprogression. Disease outcome is likely to be determined by a delicate balance between the ability of the virus to replicate and the host's ability to mount an adequate immune response. [Emphasis added by Examiner].

Huang *et al.* (1995) also performed PCR analysis on proviral DNAs obtained from long-term survivors of HIV infection. The authors reported that:

> We found that there is no gross deletion within *nef* in the cases studied; most *nef* sequences (91.1%) obtained from 10 subjects contained a full-length and intact open reading frame. In addition, **at the protein level, there were no discernible differences between the Nef consensus sequences derived from long-term survivors and those from patients with AIDS.** We therefore conclude that deletion of or gross sequence abnormality within *nef* is not likely to be a common explanation for the well-being of long-term survivors of HIV-1 infection. [Emphasis added by Examiner].

Additional studies by Michael *et al.* (1995) corroborated these findings. It was reported by this group that:

> We have studied the sequence and function of the human immunodeficiency virus type 1 (HIV-1) *nef* genes from nine patients with highly divergent rates of disease progression enrolled in a longitudinal study of HIV disease ... The *nef* gene from each of these patients was amplified and cloned, and the sequence of 8 to 10 clones was determined. Only 2 of 88 (2.3%) *nef* genes recovered from these nine patients were grossly defective. Moreover, **there was no relationship between the phylogeny of *nef* sequences and the corresponding rates of disease progression from these patients ... There was no correlation found between the functions of the *nef* genes from these patients and their corresponding rates of disease progression.** We conclude that the *nef* gene is not a common mediator of the rate of HIV disease progression in natural infection.

The prior art clearly illustrates that other viral, as well as, cellular gene products contribute to the pathogenic phenotype. Moreover, the specification asserts that changes in *nef* may contribute to disease progression, nevertheless, it is not readily manifest if each of the identified clones has been completely characterized at the molecular level and the contributions of other viral gene products and regulatory regions examined. For instance, the LTNP phenotype may result from a modification in Tat or TAR that results in lower levels of viral replication. Considering the unpredictability of the prior art, it would be premature to conclude that Nef is responsible for the LTNP phenotype, absent complete characterization of the various clones. Moreover, the findings of the prior art would preclude the skilled artisan from extending the findings of the instant application to any other HIV-1 isolate, particularly since it appears that all the clones described in the specification evolved from the same progenitor. While it is noted that the SBBC patients were all infected with viruses that share common genotypic/phenotypic characteristics (e.g., a deletion in the *nef*/LTR region). However, these arguments and data do not exclude the possibility that host factors and other viral factors may also contribute to the LTNP state in these

individuals.

2) The specification fails to provide adequate guidance concerning the selection of allelic variants of *nef* that contain the requisite phenotypic properties. This concern has not been adequately addressed by applicants' responses. The SBBC patients were all infected with the same parental virus. Thus, it is not readily manifest, given the teachings of Terwilliger *et al.* (1991), whether these findings can be extended to other HIV-1 isolates other than those described in the specification. As previously stated, it was observed in the literature that **allelic variants of *nef* provide different contributions to the replicative properties of HIV-1.** Terwilliger *et al.* (1991) reported the following:

> The effects of the viral gene *nef* on human immunodeficiency virus type 1 (HIV-1) replication in culture were investigated using *nef* alleles of the HIV-1 IIIB and ELI strains. The results demonstrate significant allelic variation in the effect of *nef* on virus replication in both an established human $CD4^+$ T-cell line and primary human lymphocytes. In the context of HXB2 virus, the ELI *nef* allele but not the IIIB *nef* allele permits initiation of efficient low-multiplicity infection in primary peripheral blood mononuclear cells, including unfractionated peripheral blood lymphocytes, T cells, and monocyte/macrophages. **Within the same genetic context, the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.** Sequences in the IIIB and ELI genomes outside of *nef* also moderate the effects of *nef* on HIV-1 replication.

In view of the teachings of the prior art, how could the skilled artisan reasonably predict which *nef* allelic variants will produce the desired LTNP phenotype?

3) The specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef*⁻ deletion variants would mount an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV infection and the clinical sequelae leading to AIDS. A number of attendant

caveats associated with the development of an efficacious HIV-1 vaccine or therapeutic were reviewed by Graham *et al.* (1995) and Haynes (1993). The rational design of an effective vaccine requires a knowledge of the pathogenesis of HIV infection and an understanding of the human correlates of protective immunity. The cruxes associated with vaccine development can be summarized as follows:

a) The correlates of human protection remain to be elucidated. Thus, it is not clear if humoral, cell-mediated, or both types of immune response will provide protection.

b) The plasticity, or quasispecies nature, of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of effective HIV-1 vaccines and therapeutics. Convincing data demonstrating that such a vaccine can neutralize diverse field isolates remains to be presented.

c) The most appropriate methods for presenting viral antigens to the immune system remains to be elucidated. Thus, it is not readily manifest which mechanisms will optimize MHC Class I- or II-dependent antigen uptake, processing, compartmentalization, and presentation.

d) The viral antigens that confer protective immunity remain to be elucidated. Thus, the skilled artisan cannot predict which immunogens (i.e., Gag, Pol, Env) should be included in a putative vaccine and the form they should take (i.e., whole viral vaccine, sub-unit).

e) The viral and cellular determinants responsible for mucosal immunity remain to be elucidated. This route of administration plays a major role in viral transmission. Any efficacious vaccine will need to generate a strong mucosal immune response, probably through the production of neutralizing secretory IgA antibodies, to prevent the mucosal transmission of HIV-1.

f) Adequate animal models are not available for vaccine efficacy

testing. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies can not be directly extrapolated to a clinical setting. Graham *et al.* (1995) specifically note (refer to pp. 1333-1334) that the **"structural differences between SIV and HIV complicate the direct translation to humans of the results of vaccine studies in the SIV-macaque system"** and that **"no animal model has been found in which an AIDS-like illness develops from a virus with the antigenic determinants of HIV-1."** It was further emphasized by Haynes (1993; refer to p. 1280) that **"In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection."**

These factors have not been adequately addressed by applicants' responses and exhibits. The reliance upon Dyer *et al.* (1999) is misdirected since the authors reported (see Abstract, p. 436) that "Proposals for the use of live attenuated human immunodeficiency virus (HIV) type 1 (HIV-1) as a vaccine candidate in humans have been based on the production afforded by attenuated simian immunodeficiency virus in the macaque model ... **it is not yet known if this strategy could succeed in humans"**. Applicants appear to be suggesting that HIV-1-specific CTL responses may confer protection against the invading pathogen. However, this study (see Abstract, p. 436) noted that "**Two of seven patients had weak CTL responses, and in one recipient, no HIV-specific CTLs were detected.**" Thus, nearly half of this sample population did not have strong HIV-1-specific CTL responses. This only illustrates the complexities associated with trying to ascertain which viral immunogens are capable of providing a protective or therapeutic immune response. Moreover, the failure to elicit strong CTL responses in these individuals may be due to the replication-impaired state of the

virus. Thus, it is not readily manifest how a replication-impaired virus that replicates to such low levels would be capable of producing a robust immune response that would lead to viral inactivation and clearance. The authors further report (see p. 441, rt. col., bridging paragraph) that "**our recent follow-up of these individuals suggests that slow disease progression may be occurring in some members with detectable viral replication. Also, declining CTLp levels in C98 suggest that CTLs may fail to adequately control viral replication in the future.**" The authors conclude (see p. 442, last paragraph) that "**We suggest that a potential vaccine candidate would require further attenuation than that in the natural SBBC viral strain ... whether such responses are capable of protecting against wild-type HIV-1 challenge remains to be determined.**" Clearly, there are a number of issues that remain to be resolved before any attenuated live HIV-1 vaccine can be utilized.

Moreover, the reliance upon Kent *et al.* (2001) is also misdirected. First, applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). Thus, this exhibit cannot be properly relied upon to demonstrate that the disclosure was enabled at the time of filing. Second, even if this exhibit was relied upon, it still fails to address a number of the defects previously noted by the Examiner. The claimed invention is directed toward a replication-impaired HIV-1 construct that contains a single deletion in the *nef*/3'LTR coding/regulatory

region. The teachings of Kent and colleagues are directed toward the SIV macaque model. The prior art has already clearly established that direct extrapolations vis-à-vis vaccine efficacy between humans and macaques cannot be performed due to the various genotypic/phenotypic differences between HIV and SIV, as well as, humans and macaques. Third, the construct employed by Kent *et al.* (2001) differed considerably from that currently claimed. The SIV macaque construct contained multiple deletions in both the 5′ LTR and 3′ *nef*/LTR as opposed to the instantly claimed construct which comprises a single *nef* mutation. This study also reported that in SIV, single deletions in the 3′ *nef*/LTR overlap region actually led to sustained infection and SAIDS. Fourth, the art clearly raises a number of concerns pertaining to the utilization of replication-impaired HIV-1 constructs as vaccine vehicles (see subsequent paragraph). Thus, this publication fails to overcome the rejection.

4) The prior art (Ruprecht *et al.*, 1995) raises a number of additional concerns pertaining to the development of an AIDS vaccine involving *nef*-deficient viruses. The findings of this article can be summarized as follows: a) SIV mutants containing *nef*, *vpr*, and negative regulatory element (NRE) deletions replicated to high levels following oral administration to infant macaques. All of the animals receiving this "vaccine" either developed SAIDS or display symptoms of the disease (Baba *et al.*, 1995). b) The *nef* gene product is not a direct molecular determinant for virulence. Nef appears to modulate the viral load while other determinants are responsible for the direct pathogenic properties of the virus. Accordingly, *nef*-deficient viruses are replication-impaired, not avirulent, and can be activated (thereby becoming virulent) by additional host, bacterial, or viral factors. c) Protective immune responses to SIV *nef* mutants developed quite slowly following administration of the putative vaccine. A

dilatory immune response in humans could facilitate spread of the disease through high risk behavior by encouraging a false sense of protection. d) Replication-impaired retroviruses still undergo integration into the host chromosome. This activity can potentially result in insertional mutagenesis. Disseminated lymphoproliferative disorders were associated with the administration of an SIV *nef* "vaccine". The authors soundly conclude (refer to page 178, final paragraph) that **"We feel that it is premature to consider *nef*-deleted viruses as candidate AIDS vaccines; they are neither safe nor sufficiently effective. The race between vaccine-virus replication and host defenses could be decided in favour of virus replication in coinfected or immunocompromised hosts."** These concerns have not been adequately addressed by applicants' arguments or accompanying exhibits. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

7. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

8. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 January, 2003